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EXAMINER	
SHEN, WU CHENG WINSTON	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,466	ANDERSON ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *272,273,280-284,289,291,296,297,313,320-324,328,331,342 and 343* is/are pending in the application.

4a) Of the above claim(s) *281,289,296,297,313,320-324,328,331,342 and 343* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *272,273,280,282-284 and 291* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/07/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/583,466 is a 371 of PCT/US04/41721 12/13/2004 which claims benefit of 60/530,043 filed on12/16/2003.

Election/Restriction

Applicant's election with traverse of Group III, claims 272-291, drawn to a method of identifying an agent that modulates a *phenotype* associated with a disruption of a gene which encodes for a PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO 1083, hu TRPM2 or PRO 1801 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of a gene which is an ortholog of a human gene that encodes for the PRO224, PRO9783, PRO1108, PRO34000, PRO240, PRO943, hu A33, PRO230, PRO178, PRO1199, PRO4333, PRO1336, PRO19598, PRO1083, hu TRPM2 or PRO1801 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal, in the reply filed on 10/30/2009 is acknowledged. In response to further restriction to a gene which encodes a specific PRO protein molecule, Applicant elected PRO224 polypeptides.

In response to further restriction to a specific genus of disease, Applicant elected eye abnormality recited in claim 273. In response to requirement of election of species, Applicant elected retinal abnormality recited in claim 280.

The traversal is on the ground(s) that the claims 272-291 (methods of identifying an agent that modulates a phenotype), 296, 297 (methods of identifying an agent that modulates a physiological characteristic), 313-331 (methods of identifying an agent that ameliorates or modulates a disorder or abnormality), and 342-343 (methods of evaluating a therapeutic agent) are all directed to subject matter related to the identification of agents that modify or affect the characteristics of animals having altered expression of particular polypeptide, which is recognized in the arts as being similar and related subject matter, and for which a search would readily identifying references related to the subject matter of all these claims. Applicant argues that a search for the subject matter of the elected Group III (claims 272-291) would necessarily also provide references related to the subject matter of other Groups, such as, Group V (claims 296, 297), Group IX (claims 313-331), and Group XVI (claims 342, 343). Such a search for the subject matter of other groups, which could be carried out along with the search for the elected Group III (claims 272-291) would not add to the search burden on the Examiner.

The traversal is not found persuasive because Applicant's amended claims encompass multiple inventions with multiple related and patentably distinct methods with distinct goals (methods of identifying an agent that modulates a phenotype, methods of identifying an agent that ameliorates or modulates a disorder or abnormality, methods of identifying an agent that ameliorates or modulates a disorder or abnormality, methods of evaluating a therapeutic agent), method steps and technical considerations (e.g. the steps and technical considerations required

for identification of an agent that modulates a phenotype are patentably distinct from the steps and technical considerations required for evaluating a therapeutic agent capable of affecting a condition), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. The common technical feature in Groups III, V, IX, and XVI is a phenotype associated with a disruption of a gene which encodes for a PRO0224. As elected invention is directed to retinal abnormality, the common technical feature in Groups III, V, IX, and XVI is a retinal abnormality phenotype associated with a disruption of a gene which encodes for a PRO0224. It is noted that the limitation "associated with" does not define a cause-and-effect relationship which requires the disruption of a gene encoding a PRO0224 results in a retinal abnormality phenotype directly. In other words, the common technical feature in Groups III, V, IX, and XVI is a retinal abnormality phenotype associated with a disruption of a gene. However, this common technical feature cannot be a special technical feature under PCT Rule 13.2 because the feature is shown in the prior art. For instance, **Upton et al.** teaches analysis of retinal projections of 5-HT_{1B} knockout, serotonin transporter knockout, serotonin transporter/5-HT_{1B} double knockout and monoamine oxidase A/5-HT_{1B} double knockout mice. Upton et al. teaches that in all four different knockout mice, the ipsilateral retinal projection to the superior colliculus was more diffuse and lost its characteristic patchy distribution. The alterations were most severe in the serotonin transporter knockout mice, where the ipsilateral retinal fibers covered the entire rostrocaudal and mediolateral extent of the superior colliculus, whereas in the 5-HT_{1B} and double knockout mice, fibers retracted from the caudal and lateral superior colliculus. Upton et al. teaches that retinal abnormalities in the 5-HT_{1B} knockout mice appeared only after postnatal day (P) 4 and treatment with parachlorophenylalanine (at P1-P12) to

decrease serotonin levels caused an exuberance of the ipsilateral retinal fibers throughout the superior colliculus. In the dorsal lateral geniculate nucleus in contrast, the distribution and size of the ipsilateral retinal projection was normal in all four knockout mice. In the serotonin transporter knockout mice however, the contralateral retinal fibers failed to retract from the mediodorsal dorsal lateral geniculate nucleus, an abnormality that was reversed by early treatment with parachlorophenylalanine andin the serotonin transporter/5-HT_{1B} double knockout (See abstract, Upton et al., Lack of 5-HT_{1B} receptor and of serotonin transporter have different effects on the segregation of retinal axons in the lateral geniculate nucleus compared to the superior colliculus, *Neuroscience*, 111(3):597-610, 2002). It is further noted that search burden is not germane to PCT lack of unity practice.

It is noted that that based on further restriction to "eye abnormality" as elected invention for prosecution, claim 289 reciting "cardiovascular disorder" is withdrawn from consideration as non-elected invention. Additionally, based on election of retinal abnormalities recited in claim 280 as elected species, claim 281 is withdrawn from consideration as non-elected species.

Claims 1-271, 274-279, 285-287, 290, 292-295, 298-312, 314-319, 325-327, 329-330, 332-341, and 344-386 are cancelled. Claims 272, 273, 280-284, 289, 291, 296, 297, 313, 320-324, 328, 331, 342, and 343 are pending.

Claims 281, 289, 296, 297, 313, 320-324, 328, 331, 342, and 343 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 272, 273, 280, 282-284, and 291 are currently under examination to the extent of a phenotype is a retinal abnormality, which is a species belongs to the genus of eye abnormality.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

1. Claim 273 is objected to for being drawn to a non-elected invention. Specifically, Applicants have elected "eye abnormality" as the phenotype associated with a disruption of a gene which encodes for a PRO0224 recited in claim 273 and as such, claim 273 and dependent claims are examined only to the extent that they read on a "eye abnormality". Applicants are required to delete the non-elected subject matter from the instant claim.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 272, 273, 280, 282-284, and 291 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

It is noted that the recited method is incomplete. The steps of claim 272 do not recite any specific phenotype of claimed non-human animal that has been modulated by identified agent. The step "(e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal" recited in claim 272 does not relate back to the preamble of the claim "identifying an agent that modulates a phenotype associated

with a disruption of a gene which encodes for a PR0224" in a positive process. Claims 273, 280, 282-284, and 291 depend from claim 272.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

3. Claims 272, 273, 280, 282-284, and 291 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed a method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PR0224 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO224 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

The nucleotide sequences that encode all PRO224, variants, and fragments thereof encompassed within the genus of a gene which encodes for a PR0224 polypeptide have not been disclosed. Based upon the prior art there is expected to be variation among the species of cDNA, which encode PRO224 polypeptide, because the sequence of PRO224 cDNAs would be expected to vary among individuals. The specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that encodes a human PR0224 polypeptide (SEQ ID No: 2) from an unknown human cell type (See paragraphs [0230], SEQ ID No: 1 and SEQ ID No: 2, US 2007/0292438, publication of instant application). The specification discloses that in knockout experiments, the gene encoding PRO224 polypeptides (designated as DNA33221-1133) [UNQ198] was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019421 or *Mus musculus* hypothetical protein 425018-1, protein reference: NP_062294 or hypothetical protein 425018-1; putative VLDL lipoprotein receptor precursor; DNA segment, Chr 17, ERATO Doi 716, expressed [*Mus musculus*]; the human gene sequence reference: BC007083 or *Homo sapiens*, 8D6 antigen, clone MGC: 14623 IMAGE: 4076237; the human protein sequence corresponds to reference: NP_057663 or 8D6 antigen (*Homo sapiens*) (See paragraphs [0699] and [0700], US 2007/0292438, publication of instant application). The specification does not provide any information pertaining to the *structure-function relationship* between SEQ ID NO: 1 (which encodes human PRO224 cDNA), mouse DNA33221-1133 (UNQ198), and any other gene encoding a PRO224 polypeptide encompassed by the genus of a gene which encodes for a PRO224 polypeptide. There is no evidence on the record of a relationship between the structures of SEQ ID NO: 1 cDNA and the mouse DNA33221-1133 (UNQ198) that would provide any

reliable information about the structure of other DNAs encoding a PRO224 polypeptide within the genus. There is no evidence on the record that the asserted human PRO224 cDNA had a known structural relationship to any other PRO224 cDNA sequences; the specification discloses only a single human PRO224 cDNA obtained from an undisclosed origin of human cells; the art indicated that there is variation between a given polypeptide cDNA sequences and their functions. The specification has not even disclosed the function of PRO224 that the claimed cDNA encodes. There is no evidence of record that would indicate that any of the claimed variants and fragments of SEQ ID NO: 1, even have the biological activity of a PRO224 polypeptide. In the absence of a functional assay it would not be possible to test variants of the claimed sequences for biological activity of a PRO224 polypeptide encoded by a gene. In fact, the specification does not disclose any function and/or domain structure of PRO224 polypeptide. Also with regard to the claimed allelic variants, the skilled artisan cannot envision the structure of such a variant because such variants are randomly produced in nature, and cannot be predicted from a known sequence. The specification does not teach any characteristics of an "allelic" variant that would distinguish it from a non-natural variant constructed by the hand of man. In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus, because a human PRO224 cDNA sequence (i.e. SEQ ID NO: 1) is not representative of the claimed genus. Consequently, since Applicant was in possession of only the human PRO224 cDNA and since the art recognized variation among the species of the genus of cDNAs that encode PRO224 polypeptide, the human PRO224 polypeptide cDNA was not representative of the claimed genus. Therefore, Applicant was not in possession of the genus of lipase cDNAs as

encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Enablement

4. Claims 272, 273, 280, 282-284, and 291 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The nature of the invention is directed to are directed a method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PR0224 polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO224 polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

The breadth of the invention encompasses a method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PR0224 polypeptide, the method comprising: (a) providing any non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PRO224 polypeptide; (b) measuring any physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent

modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

With regard to any non-human transgenic animal, the specification discloses isolation of a nucleotide sequence (SEQ ID NO: 1) that encodes a human PR0224 polypeptide (SEQ ID No: 2) from an unknown human cell type (See paragraphs [0230], US 2007/0292438, publication of instant application). In this regard, it is noted that the human PRO224 cDNA (SEQ ID No: 1) cannot be disrupted in a non-human transgenic animal because the human gene is not present in the genome of a non-human transgenic animal. The specification does not disclose any information regarding the presence of human PRO224 cDNA in the genome of any non-human transgenic animal, which may be then disrupted as required by the claimed methods. With regard to transgene integration, the art taught that the site of integration is uncontrolled and yet is critical due to the possibility of integration into a silent locus. The site of integration may also result in altered tissue specificity, although the promoter used behaves differently at its normal chromosomal localization, with neighboring regulatory elements potentially influencing the transcriptional activity of the transgene (See pg. 159 col. 1 parag. 3, lines 1-7, **Ristevski**, Making better transgenic models: conditional, temporal, and spatial approaches. *Mol Biotechnol.* 29(2): 153-63, 2005). This is known as chromosomal position effects, where host sequences surrounding the site of transgene integration could alter the expected expression pattern, turning it ectopic or not detectable (See pg 39, col. 1, **Montoliu**, Gene transfer strategies in animal transgenesis. *Cloning Stem Cells.* 4(1): 39-46, 2002).

Furthermore, the status of art indicates that generation of non-human transgenic animal is unpredictable. With regard to mammalian ES cells, it is important to note that **Clark (1998)**

clearly discloses that, in principle, then, ES cells would seem the ideal candidate from which to develop an alternative route to transgenesis in live stock. However, despite intensive efforts, no validated ES cells other than mouse ES cells (i.e., cells that will contribute to the germline) have been described for any species of livestock (See right column, page 339, Clark et al., The mammary gland as a bioreactor: expression, processing, and production of recombinant proteins, *J Mammary Gland Biol Neoplasia.* 3(3):337-50, 1998). Consistent with the notion regarding unpredictability of gene targeting in mammalian ES cells other than mouse ES cells, **Williams (2003)** states that "While it has been suggested that a better understanding of the properties of embryonic stem cells could be achieved by work in the mouse and other animals, it is already clear that there are many differences between species in the properties of these cells" (See middle column, page R210, Williams, Death of Dolly marks cloning milestone, *Curr Biol.* 13(6):R209-10, 2003). At the time of filing, the art teaches that the only known non-human animal in which ES cells can be obtained was for mouse. This is because mice are the only mammals in which ES cells can be generated and which chimerism from ES cells extend to the germline (See abstract and page 2, 2nd col., 1st paragraph under "The need for nuclear transfer", **Denning et al**, New frontiers in gene targeting and cloning: success, application and challenges in domestic animals and human embryonic stem cells. 2003, *Reproduction* 126: 1-11, 2003).

With regard to any phenotype and/or physiological characteristic of a transgenic mouse, the specification discloses that in knockout mouse experiments, the gene encoding PRO224 polypeptides (designated as DNA33221-1133) [UNQ198] was disrupted. The gene specific information for these studies is as follows: the mutated mouse gene corresponds to nucleotide reference: NM_019421 or *Mus musculus* hypothetical protein 425018-1, protein reference: NP_

062294 or hypothetical protein 425018-1; putative VLDL lipoprotein receptor precursor; DNA segment, Chr 17, ERATO Doi 716, expressed [*Mus musculus*]; the human gene sequence reference: BC007083 or *Homo sapiens*, 8D6 antigen, clone MGC: 14623 IMAGE: 4076237; the human protein sequence corresponds to reference: NP_057663 or 8D6 antigen (*Homo sapiens*) (See paragraphs [0669] and [0700], US 2007/0292438, publication of instant application). The specification discloses phenotypic Analysis (for Disrupted Gene: DNA33221-1133 (UNQ198) as follows: Procedure: A cohort of 4 wild type, 4 heterozygotes and 8 homozygotes were tested in this assay. Optic fundus photography was performed on conscious animals using a Kowa Genesis small animal fundus camera modified according to Hawes and coauthors (Hawes et al., 1999 Molecular Vision 1999; 5:22). Intra-peritoneal injection of fluorescein permitted the acquisition of direct light fundus images and fluorescent angiograms for each examination. In addition to direct opthalmological changes, this test can detect retinal changes associated with systemic diseases such as diabetes and atherosclerosis or other retinal abnormalities. Pictures were provided of the optic fundus under normal light. The angiographic pictures allowed examination of the arteries and veins of the eye. In addition an artery to vein (A/V) ratio was determined for the eye (See paragraphs [0708], US 2007/0292438, publication of instant application). Ophthalmology analysis was performed on generated F2 wild type, heterozygous, and homozygous mutant progeny using the protocol described above. Specifically, the A/V ratio was measured and calculated according to the fundus images with Kowa COMIT+ software. This test takes color photographs through a dilated pupil: the images help in detecting and classifying many diseases. The artery to vein ratio (A/V) is the ratio of the artery diameter to the vein diameter (measured before the bifurcation of the vessels). The specification states that

many diseases will influence the ratio, i.e., diabetes, cardiovascular disorders, papilledema, optic atrophy or other eye abnormalities such as retinal degeneration (known as retinitis pigmentosa) or retinal dysplasia, vision problems or blindness. Thus, phenotypic observations which result in an increased artery-to-vein ratio in homozygous (-/-) and heterozygous (+/-) mutant progeny compared to wildtype (+/+) littermates would be indicative of such pathological conditions (See paragraphs [0709], US 2007/0292438, publication of instant application). The specification discloses the Results as follow: In this study, *the (-/-) and (+/-) mice exhibited an increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates indicating retinal degeneration*. The specification states that, in summary, by knocking out the gene identified as DNA33221-1133 encoding PRO224 polypeptides, both heterozygous and homozygous mutant progeny exhibit phenotypes which are associated with retinal degeneration. Such detected retinal changes are most commonly associated with cardiovascular systemic diseases or disorders that may be related to the vascular disease of hypertension (and any disease that causes hypertension, e.g. atherosclerosis), diabetes or other ocular diseases corresponding to opthalmological disorders such as retinal degeneration. Thus, antagonists of PRO224 encoding genes would lead to similar pathological retinal changes, whereas agonists would be useful as therapeutic agents in the treatment of hypertension, atherosclerosis or other opthamological disorders including retinal degeneration and diseases associated with this condition (as indicated above) (See paragraphs [0710], Example 18, US 2007/0292438, publication of instant application).

It is worth noting that the claimed methods require "identifying an agent that modulates a phenotype associated with disruption of a gene which encodes for a PRO224". However, the

specification does not provide any information regarding any agent that can reverse/modulate the increased mean artery-to-vein (A/V) ratio when compared with their (+/+) littermates exhibited by the (-/-) and (+/-) mice, which Applicant asserts to be an indication of retinal degeneration. Pertaining to this issue, as discussed in the rejection under 35 U.S.C 112 second, the steps of claim 272 do not recite any specific phenotype of claimed non-human animal that has been modulated by identified agent. The step "(e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal" recited in claim 272 does not relate back to the preamble of the claim "identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PR0224" in a positive process. Furthermore, the status of art indicates that there is no clear association, as Applicant asserts, between a phenotype of retinal abnormality (retinal degeneration) and a physiological characteristic of increased mean artery-to-vein (A/V) ratio. In this regard, **Upton et al.** teaches retinal abnormalities observed in 5-HT_{1B} knockout, serotonin transporter knockout, serotonin transporter/5-HT_{1B} double knockout and monoamine oxidase A/5-HT_{1B} double knockout mice (See abstract, Upton et al., Lack of 5-HT_{1B} receptor and of serotonin transporter have different effects on the segregation of retinal axons in the lateral geniculate nucleus compared to the superior colliculus, *Neuroscience*, 111(3):597-610, 2002). Upton et al. does not disclose any association between retinal abnormality and increased mean artery-to-vein (A/V) ratio.

Furthermore, the status of art at the time of filing as well as at present indicates that the phenotype of transgenic animal, including transgenic mouse, is unpredictable. **Matthaei** teaches that although genetic manipulations in mice have provided a powerful tool for investigating gene

function *in vivo*, recent studies have uncovered a number of developmental phenomena that complicate the attribution of phenotype to the specific genetic change. Matthaei further teaches further complications in interpretation due to unexpected epigenetic effects involving transfer of RNA or protein in oocytes or sperm (See abstract, Matthaei, Genetically manipulated mice: a powerful tool with unsuspected caveats. *J Physiol.* 582(Pt 2):481-8, 2007). Matthaei teaches that the site at which the DNA is integrated is random, as are the number of copies of the transgene. Although the expression of the construct is faithful for the promoter, on many occasions it may also be significantly influenced by the local environment at the integration site (the 'position' effect). This can lead to the promiscuous expression of the transgene (often referred to as 'leakiness'), due to modification of the specificity of the promoter, or at times to a more severe phenotype, due to disruption of an unknown gene by insertion of the transgene (insertional mutagenesis). Furthermore, Matthaei teaches that a number of different 'founder' animals with different copy numbers and different integration sites must therefore be assessed in order to determine the correct/faithful expression of each transgene, and surprisingly, in one example, 24 different founders resulted in 24 different expression patterns making it impossible to determine which pattern was correct (See right column, page 481, *J Physiol.* 582(Pt 2):481-8, 2007).

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 272, 273, 280, 282-284, and 291.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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